PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 33134/PC/ACB	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/SI2004/000019	International filing date *(day/month/year)* 09.04.2004	Priority date *(day/month/year)* 11.04.2003
International Patent Classification (IPC) or national classification and IPC C07D207/34		
Applicant LEK PHARMACEUTICALS D.D. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.12.2004	01.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Von Daacke, A Telephone No. +49 89 2399-8286

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SI2004/000019

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-14	as originally filed

Claims, Numbers

2, 6-10, 12-15, 18-22, 24-33	as originally filed
1, 3-5, 11, 16, 17, 23	filed with telefax on 06.05.2005

Drawings, Sheets

1-5	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1,3,4,5,11,15,16,17,23
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SI2004/000019

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,3-9,11-33
	No:	Claims	2,10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	1-33
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

I BASIS OF THE OPINION

The amendment to Claims 1,3,4,5,11,15,16,17 and 23, i.e. the introduction of the term "non-cyclic" has no basis in the documents as originally filed in the sense that the term as such cannot be found. Even though the disclosed species are all non-cyclic, the limitation as such is not disclosed. Hence, the Report (Sections II, V and VIII) is based on the documents as originally filed.

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

D1: WO 02/059087 A (LEK TOVARNA FARMACEVTSKIH ; SORSAK GORAZD (SL)) 1 August 2002 (2002-08-01)

D2: WO 03/018547 A (SARIN G S ; SINGH J (IN); SURI SANJAY (IN); BANSAL B R (IN); MOREPEN L) 6 March 2003 (2003-03-06)

D3: WO 01/42209 A (LEK TOVARNA FARMACEVTSKIH ; PFLAUM ZLATKO (SI)) 14 June 2001 (2001-06-14)

D4: WO 02/057228 A (GANESH SAMBASIVAM ; JOY MATHEW (IN); BIOCON INDIA LTD (IN)) 25 July 2002 (2002-07-25)

D5: WO 97/03960 A (WARNER LAMBERT CO ; LIN MIN (US); SCHWEISS DIETER (US)) 6 February 1997 (1997-02-06)

D6: WO 00/71116 A (THAPER RAJESH KUMAR ; KUMAR YATENDRA (IN); RANBAXY LAB LTD (IN); KUMAR) 30 November 2000 (2000-11-30)

have been considered for the examination procedure.

2. NOVELTY

The subject-matter of Claims 2 and 10 is anticipated by D1 (Article 33(2) PCT). D1 discloses process parameters which are all mentioned on pages 6-9 of D1.
For example, tetrahydrofuran as non-hydroxylic solvent (page 6/ line 26), toluene or cyclohexane as cyclic hydrocarbon (7/2 and 8/9, respectively), water (7/36), calcium acetate or chloride (8/30-31). Although phase separation takes place in the D1

process before adding the calcium salt, the aqueous phase includes at least traces of e.g. toluene or cyclohexane and tetrahydrofuran because all of these sovents are partially soluble also in water. Thus, the present wording of Claim 1 is not appropriate to establish novelty in view of D1. The Applicants argumentation is based on the different amounts of solvents used in D1 vis-à-vis the present application. This feature is, however, not reflected in the said claims.

3. INVENTIVE STEP

The claimed subject-matter does not fulfil the requirements of Article 33(3) PCT for the following reasons.
The closest state of the art for the present application is represented by D1 and D2. Both documents, as well as the other cited documents refer to the process for the preparation of amorphous calcium salt of Atorvastatin. Claim 1 differs from the process as described in D1 that chlorinated solvents are not mentioned and from the process of D2 that the calcium source is hydroxide and not chloride or acetate. Thus, the presently claimed processes, if at all novel, are just new combinations of well known measures concerning the choice of solvents. It is well known that Atorvastatin is soluble in chlorinated solvents such as chloroform, methylene chloride etc. (D2, p.3,l.5-6) or non-hydroxy solvents such as tetrahydrofurane or mixtures thereof (D1). The precipitation from solutions by adding an anti-solvent such as diisopropylether is known from e.g. D1-D4, The presence of water and the claimed calcium source are known from e.g.D1 (see above). Further documents disclose thew use of solvent mixtures such as tetrahydrofurane/toluene (D5) or cyclohexane as claimed cyclic hydrocarbon solvent (D6, page 4).
Thus, the features as claimed in the independent Claims 1,2 and 11 are already known from the cited prior art. As with the processes according to the cited documents amorphous Atorvastatin is prepared from solutions containing the necessary ingredients, as it is the case in the processes according to the present application, it cannot be seen which parameter of the claimed processes may be considered as forming the basis of an inventive effect.
Therefore, the problem underlying the present application should be seen in the provision of new process for the preparation of amorphous Atorvastatin calcium having unexpected properties over those of the closest prior art compounds (D1 and

D2). In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not. In the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compounds of the present application having the maximum structural similarity with the compounds of the closest prior art, such that the effect is shown to have its origins in the distinguishing feature of the claimed invention.
The Applicants argumentation is based on the alleged effect that sodium Atorvastatin is entirely soluble in the solvent system used. This feature is, however, completely absent in Claims 1 and 2 and also not taken into account in Claim 11. Thus, an inventive step can still not be recognized.
It is pointed out that the X-ray powder diffractograms of the present application (at least 1/5) are not different from that of D2. Furthermore, if the X-ray powder diffractogram of D1 is considered as originating from a non-crystalline but not entirely amorphous form of calcium Atorvastatin, the present diffractograms should be regarded in the same sense, i.e. originating from a non-crystalline but not entirely amorphous form of calcium Atorvastatin. See the peaks 2-Theta = around 18, 19, 20.5 etc..

4. INDUSTRIAL APPLICABILITY

No objection.

VIII CERTAIN OBSERVATIONS (CLAIMS)

Due to the expressions "chlorinated organic solvent" (cat.1), "non-hydroxylic organic solvent" (cat.2) and "cyclic hydrocarbon solvent" (cat.3) the claims are not clear. The solvents form an overlapping part, e.g. chlorobenzene is of cat. 1, 2 and 3, cyclohexane is of cat. 2 and 3 etc. (Article 6 PCT).

NEW CLAIMS: 1, 3, 4, 5, 11, 15, 16, 17, 23

1. A process for the preparation of amorphous atorvastatin calcium, which comprises preparation of calcium salt of atorvastatin in a mixture of solvents consisting of a non-cyclic chlorinated organic solvent, a non-hydroxylic organic solvent, and water and at which the source of calcium ions is selected from the group consisting of calcium acetate and calcium chloride.

3. A process for the preparation of amorphous atorvastatin calcium according to claim 1, characterized in that the non-cyclic chlorinated organic solvent is selected from the group consisting of chloroform, trichloroethane, dichloromethane and tetrachloroethane.

4. A process for the preparation of amorphous atorvastatin calcium according to claim 3, characterized in that the non-cyclic chlorinated organic solvent is chloroform.

5. A process for the preparation of amorphous atorvastatin calcium according to claim 3, characterized in that the non-cyclic chlorinated organic solvent is dichloromethane.

11. A process for the preparation of amorphous atorvastatin calcium which comprises:

a) preparation of a neutral reaction mixture containing sodium salt of atorvastatin,
b) addition of non-cyclic chlorinated organic solvent selected from the group consisting of dichloromethane, trichloroethane, tetrachloroethane and chloroform, or addition of cyclic hydrocarbon solvent selected from the group consisting of cyclohexane, cyclopentane, and methyl cyclohexane,
c) addition of an equivalent or an excess quantity of calcium ions source selected from the group consisting of calcium acetate and calcium chloride,
d) isolation of atorvastatin calcium.

15. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the non-cyclic chlorinated organic solvent is

selected from the group consisting of chloroform, trichloroethane, dichloromethane, and tetrachloroethane.

16. A process for the preparation of amorphous atorvastatin calcium according to claim 15, characterized in that the non-cyclic chlorinated organic solvent is chloroform.

17. A process for the preparation of amorphous atorvastatin calcium according to claim 15, characterized in that the non-cyclic chlorinated organic solvent is dichloromethane.

23. A process for the preparation of amorphous atorvastatin calcium according to claims 11, characterized in that simultaneously with an addition of the non-cyclic chlorinated organic solvent or cyclic hydrocarbon solvent also a 0.5fold to a twofold quantity of saturated aqueous solution of sodium chloride with respect to the existing volume of the solution is added.